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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB95/02846 (22) International Filing Date: 6 December 1995 (06.12.95) (30) Priority Data: 9424694.9 7 December 1994 (07.12.94) GB (71) Applicants (for all designated States except US): THE WELLCOME FOUNDATION LIMITED [GB/GB]; Uni- com House, 160 Euston Road, London NW1 2BP (GB). KING'S COLLEGE LONDON [GB/GB]; The Strand, London WC2R 2LS (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DE BELDER, Adam, Ju- lian [GB/GB]; King's Healthcare, King's College School of Medicine and Dentistry, Denmark Hill, London SE5 9RS (GB). LEES, Christoph, Christopher [GB/GB]; King's Healthcare, King's College School of Medicine and Den- tistry, Denmark Hill, London SE5 9RS (GB). MARTIN, John [GB/GB]; King's Healthcare, King's College School of Medicine and Dentistry, Denmark Hill, London SE5 9RS (GB). (74) Agent: FRANK B. DEHN & CO.; Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).	(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>	
(54) Title: USE OF A NITRIC OXIDE (NO) DONOR FOR THE TREATMENT OF HYPERTENSION DURING PREGNANCY		
(57) Abstract The use of a NO donor for the prophylaxis and/or treatment of hypertension and hypertensive disorders during pregnancy, in particular for the prophylaxis and/or treatment of pre-eclampsia, is disclosed. Preferably, the NO donor is an S-nitroso compound of the formula R-SNO wherein R is one or more amino acid derived fragments.		

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USE OF A NITRIC OXIDE (NO) DONOR FOR THE TREATMENT OF HYPERTENSION DURING PREGNANCY

The present invention relates to the use of a nitric oxide (NO) donor for the treatment of hypertension during pregnancy, in particular for the treatment of pre-eclampsia.

5 Pre-eclampsia is a multiorgan disease which is unique to human pregnancy. The condition is characterised by the development of elevated blood pressure, proteinuria, and generalised oedema. Pre-eclampsia occurs after 20 weeks of gestation, but most usually after 32 weeks, and accounts for more than 50% of all the hypertensive disorders of pregnancy. It is a major cause of foetal and
10 maternal morbidity and mortality.

The cause of pre-eclampsia is not clearly understood. Plasma levels of aldosterone and renin are lower than in normal pregnant individuals but still may be inappropriately high in relation to salt intake and volume status. A decrease in plasma volume and haemoconcentration is typically observed. Some have
15 suggested (Internal Medicine, 4th Edition, Part 10, p 2816-2817 (1994)) that this increase in vascular tone is caused by a relative or absolute deficiency in the production of the vasodilating prostaglandin, PGI₂ (prostacyclin). It has also been suggested (Textbook of Medicine, 19th Edition, Vol. 1, p600-601 (1992)) that abnormalities in eicosanoid metabolism may play a role in the pathogenesis
20 of pre-eclampsia, reflecting an imbalance between production of vasodilating prostacyclin and the vasoconstrictor effects of thromboxane.

Pre-eclampsia can be an extremely severe disease and it can be clinically useful to separate the disease into mild and severe cases. The criteria frequently used to indicate severe disease is given in Internal Medicine (supra). In most cases,
25 the development of severe pre-eclampsia requires delivery, regardless of gestational age. Even in mild cases of the disease, careful monitoring is required because of the possibility of rapid deterioration. A subset of severe pre-eclamptic patients develop haemolysis (H), elevated liver enzymes (EL), and low platelets (LP), the so-called "HELLP Syndrome". These patients frequently
30 have little blood pressure change and limited symptoms. The disease is characterised by rapid deterioration and death if prompt delivery and aggressive supportive therapy are not implemented.

Present methods of treatment depend on the severity of the condition. For women with mild disease who are remote from term, total bed rest. In cases of severe pre-eclampsia, delivery is generally required, once blood pressure has been controlled.

5 It has been advocated by some that low-dose aspirin (60-80 mg/day) throughout pregnancy for patients at increased risk of developing pre-eclampsia is beneficial. However, in a recent paper (BMJ, 308, 1250-1251, 14 May 1994), the results of a multicentre trial looking at the use of low dose aspirin in
10 pregnancy were discussed. The theoretical basis of the benefit of aspirin is believed to be its suppression of thromboxane synthesis, which results in less placental aggregation and therefore less placental ischaemia thought to underlie impaired foetal growth and the clinical features of pre-eclampsia. Concern had been expressed about the potential toxicity of such a potent anti-platelet drug for
15 mothers and fetuses. The authors of the paper conclude from the results obtained that there is no justification in the routine prophylaxis or the therapeutic use of antiplatelet treatment in all pregnant women who are at risk of pre-eclampsia. Consequently there is still no really effective means of preventing or controlling pre-eclampsia.

20 It has now been found that NO donors are of use in the prophylaxis and control of hypertension during pregnancy. Accordingly the present invention provides the use of a NO donor in the manufacture of a medicament for the prophylaxis and/or control of hypertension during pregnancy.

25 Alternatively there is provided a method of prophylaxis and/or control of hypertension during pregnancy comprising administering to a patient in need thereof a therapeutically effective amount of a NO donor.

By the term NO donor is meant a compound which is capable of liberating NO in the body.

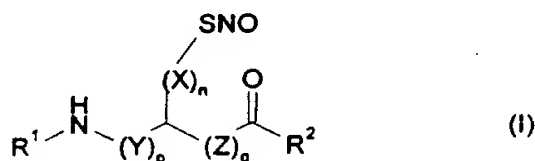
30 Hypertensive disorders encountered during pregnancy include pre-eclampsia, eclampsia, chronic hypertension ($\geq 140/90$ mm Hg), chronic hypertension with superimposed pre-eclampsia/eclampsia, and late or transient hypertension. In particular the present invention may be used for the prophylaxis and/or treatment of pre-eclampsia.

The compounds of the present invention may also be used for women suffering from HELLP syndrome and accordingly such use provides a further aspect of the present invention.

Accordingly the present invention further provides the use of NO donor in the prophylaxis and/or treatment of pre-eclampsia. Alternatively, there is provided a method of prophylaxis and/or treatment of pre-eclampsia comprising administering to a patient in need thereof a therapeutically effective amount of an NO donor.

By the term "NO donor" is meant any compound which is capable of liberating NO *in vivo*. Whilst any compound which is a NO donor can be used according to the present invention, a preferred group of compounds are S-nitroso compounds of the formula R-SNO wherein R is one or more amino acid derived fragments.

In one aspect, the NO donors of the present invention are a group of compounds of formula (I).



wherein

n is 0 or 1; X is a C_{1-6} straight or branched alkylene chain;

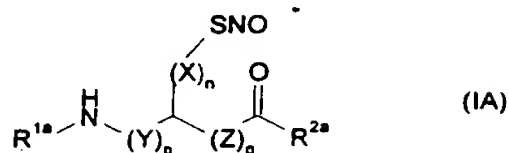
p and q are independently 0 or 1; Y and Z may be the same or different and are each a C_{1-4} hydrocarbyl chain optionally substituted by one or more groups R^4 and R^5 wherein R^4 and R^5 may be the same or different and are selected from hydrogen, C_{1-4} alkyl or C_{6-10} aryl;

R^1 is hydrogen or a group COR^3 , wherein $\text{R}^3\text{CO}_2\text{H}$ is a natural L-amino acid (other than cysteine) and/or the D-isomer thereof;

R^2 is OH or a group NR^6R^7 , wherein HNR^6R^7 is a natural L-amino acid (other than cysteine) and/or the D-isomer thereof;

or salts, esters or amides thereof.

In a further aspect, the NO donors of the present invention are a group of compounds of formula (IA)



wherein n, p, q, X, Y and Z are as hereinbefore defined;

5 R^{1a} is hydrogen or a group COR^{3a} wherein R^{3a} is a C_{1-8} hydrocarbyl group which is optionally substituted by one or two substituents which may be the same or different and are selected from OH, COOH, NH_2 ;

10 R^{2a} is OH or a group $\text{NR}^{6a}\text{R}^{7a}$ wherein R^{6a} is a C_{1-8} hydrocarbyl group which is optionally substituted by one or two substituents which may be the same or different and are selected from OH, COOH, NH_2 or a C_{1-4} alkyl group optionally substituted by COOH; and R^{7a} is hydrogen or a C_{1-8} hydrocarbyl group which is optionally substituted by one or two substituents which may be the same or different and are selected from OH, COOH, NH_2 or a C_{1-4} alkyl group optionally substituted by COOH; or R^{6a} and R^{7a} may be joined to form a 5- or 6- membered heterocyclic ring;

or salts, esters or amides thereof.

A particularly preferred NO donor for use according to the present invention is S-nitroso-glutathione (GSNO) or all salts, esters and amides thereof.

20 In addition to the above compounds, glyceryl trinitrate may be of use in the prophylactic treatment of pre-eclampsia and other hypertensive conditions.

Whilst it may be possible for the NO donors to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. According to a further aspect, the present invention provides a pharmaceutical formulation comprising a NO donor as hereinbefore defined or a pharmaceutically acceptable salt, ester or amide thereof, together with one or more pharmaceutically acceptable carriers therefor and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intravenous and intraarticular), rectal, vaginal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a NO donor or a pharmaceutically acceptable salt, ester or amide thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the

addition of the sterile liquid carrier, for example, saline, or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

- 5 Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

- 10 Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Compositions for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

- 15 Preferred unit dosage formulations are those containing an effective dose, as herein below recited, or an appropriate fraction thereof, of the active ingredient.

- 20 It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

- 25 The effective amount of active ingredient required is from 5 $\mu\text{g/day}$ to 1mg/day, suitably 50 $\mu\text{g/day}$ to 500 $\mu\text{g/day}$, depending on the particular NO donor administered. Suitably, sufficient compound is given which will liberate 2 μmol to 0.5mmol of NO/day. Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose.

The NO donors are suitably administered, orally, by injection (intravenous or subcutaneous), by infusion, or vaginally.

The present invention will now be described by way of example only:

Method

Six women whose pregnancies ranged from 23 to 31 weeks of gestation were studied. All women fulfilled the criteria for pre-eclampsia, namely, proteinuria and hypertension. In addition to this, all babies were growth retarded (abdominal circumference <5th centile for gestation) and all women had high resistance uterine artery perfusion.

All women were already taking maximal oral antihypertensive therapy (methyldopa or nifedipine).

Patients were placed recumbent in a quiet dark room and received a 45 - 90 minute GSNO infusion through a vein in the antecubital fossa. The minimum dose of GSNO used was 50 µg/min, maximum was 250 µg/min. Blood was collected for platelet activation studies through a cannula placed in the opposite antecubital fossa. Blood pressure and pulse was recorded every 10 minutes while the infusion proceeded, and uterine and fetal Doppler waveforms were obtained using an Acuson 128 (Acuson Ltd, Mountainview, CA.) ultrasound machine.

Platelet activation was assessed by IIbIIIa and p-selectin expression.

Results

Blood pressure: All women showed a reduction in arterial blood pressure (Figure 1).

Platelet Activation: In 5 out of 6 women, platelet activation was raised before the start of GSNO infusion. In all 5 cases, platelet activation was returned to baseline levels after GSNO infusion.

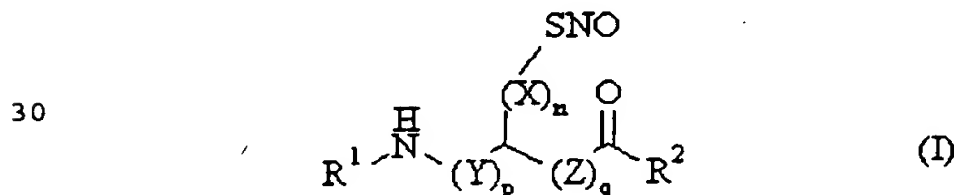
Fetal Dopplers: Despite the fall in mean arterial blood pressure, there was no change in the foetal circulation assessed by Doppler ultrasound at any dose of GSNO.

Uterine Dopplers: Uterine blood flow remained unchanged throughout GSNO infusion in 5 out of the 6 women, however in one

there was a dramatic improvement in diastolic flow as assessed by uterine resistance and pulsatility indices.

Claims

1. The use of a NO donor in the manufacture of a
5 medicament for the prophylaxis and/or control of
hypertension and/or hypertensive disorders during
pregnancy.
2. The use according to claim 1 wherein the
10 hypertensive disorder is pre-eclampsia.
3. The use according to claim 1 wherein the
hypertensive disorder is HELLP syndrome.
4. The use of a NO donor in the manufacture of a
15 medicament for the prophylaxis and/or treatment of pre-
eclampsia.
5. The use according to any of the preceding claims
20 wherein the NO donor is a S-nitroso compound of the
formula R-SNO wherein R is one or more amino acid
derived fragments.
6. The use according to any one of the preceding
25 claims wherein the NO donors of the present invention
are a group of compounds of formula (I)



wherein

35

n is 0 or 1; X is a C₁₋₆ straight or branched alkylene
chain;

- 10 -

p and q are independently 0 or 1; Y and Z may be the same or different and are each a C₁₋₄ hydrocarbyl chain optionally substituted by one or more groups R⁴ and R⁵ wherein R⁴ and R⁵ may be the same or different and are selected from hydrogen, C₁₋₄ alkyl or C₆₋₁₀ aryl;

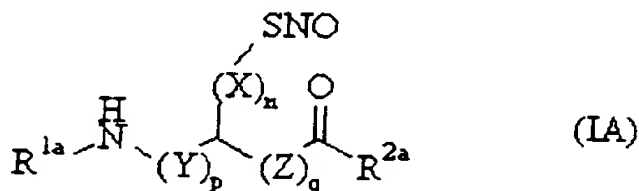
R¹ is hydrogen or a group COR³, wherein R³CO₂H is a natural L-amino acid (other than cysteine) and/or the D-isomer thereof;

R² is OH or a group NR⁶R⁷, wherein HNR⁶R⁷ is a natural L-amino acid (other than cysteine) and/or the D-isomer thereof;

or a salt, ester or amide thereof.

7. The use according to any one of claims 1 to 5 wherein the NO donors of the present invention are a group of compounds of formula (IA)

20



25

wherein n, p, q, X, Y and Z are as defined in claim 6;

R^{1a} is hydrogen or a group COR^{3a} wherein R^{3a} is a C₁₋₈ hydrocarbyl group which is optionally substituted by one or two substituents which may be the same or different and are selected from OH, COOH, NH₂;

R^{2a} is OH or a group NR^{6a}R^{7a} wherein R^{6a} is a C₁₋₈ hydrocarbyl group which is optionally substituted by one or two substituents which may be the same or different and are selected from OH, COOH, NH₂ or a C₁₋₄ alkyl group optionally substituted by COOH; and R^{7a} is hydrogen or a

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C₁₋₈ hydrocarbyl group which is optionally substituted by one or two substituents which may be the same or different and are selected from OH, COOH, NH₂ or a C₁₋₄ alkyl group optionally substituted by COOH; or R^{6a} and R^{7a} may be joined to form a 5- or 6- membered heterocyclic ring;

or a salt, ester or amide thereof.

8. The use according to any preceding claim wherein the NO donor is S-nitroso-glutathione (GSNO) or any salt, ester or amide thereof.

9. The use according to any one of claims 1 to 4 wherein the NO donor is glyceryl trinitrate.

10. A method of prophylaxis and/or controlling hypertension and/or hypertensive disorders during pregnancy comprising administering to a mammal in need thereof an effective amount of a NO donor.

11. A method according to claim 10 wherein the hypertensive disorder is pre-eclampsia.

12. A method according to claim 10 wherein the hypertensive disorder is HELLP syndrome.

13. A method of prophylaxis and/or treatment of pre-eclampsia comprising administering to a mammal in need thereof an effective amount of a NO donor.

14. A method according to any one of claims 10 to 13 wherein the NO donor is a S-nitroso compound of the formula R-SNO wherein R is one or more amino acid derived fragments.

15. A method according to any one of claims 10 to 14 wherein the NO donor is a compound of formula (I) as

- 12 -

defined in claim 6.

5 16. A method according to any one of claims 10 to 14 wherein the NO donor is a compound of formula (Ia) as defined in claim 7.

10 17. A method according to any one of claims 10 to 16 wherein the NO donor is S-nitroso-glutathione (GSNO) or any salt ester or amide thereof.

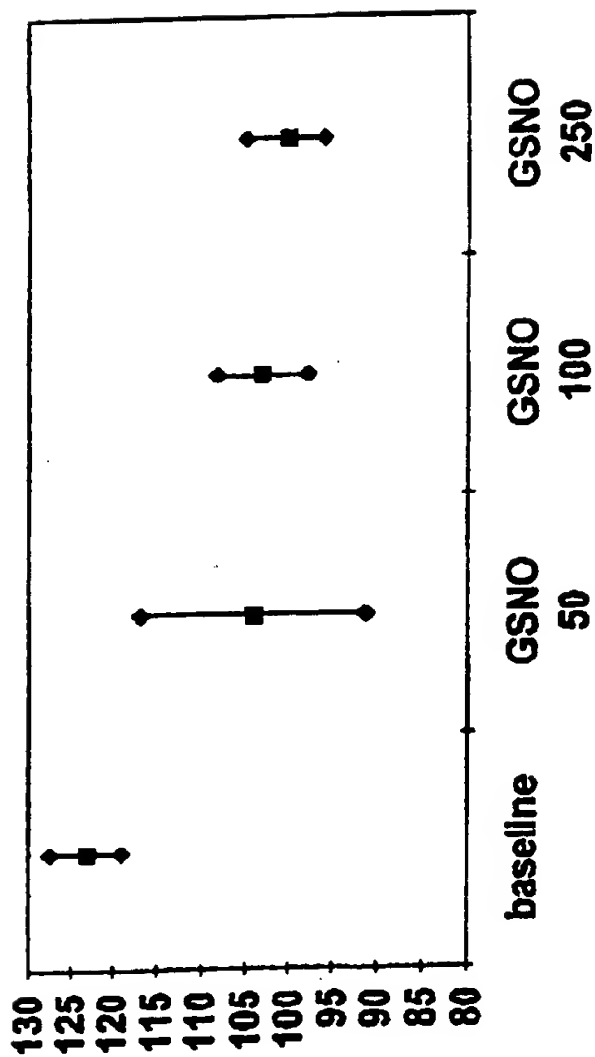
18. A method according to any one of claims 10 to 13 wherein the NO donor is glyceryl trinitrate.

15 19. A pharmaceutical composition for the prophylaxis and/or control of hypertension and/or hypertensive disorders during pregnancy which comprises a NO donor together with one or more pharmaceutically acceptable carriers thereof.

20 20. A pharmaceutical composition for the prophylaxis and/or treatment of pre-eclampsia which comprises a NO donor together with one or more pharmaceutically acceptable carriers thereof.

FIGURE 1

Changes in mean arterial pressure \pm SEM in six women with pre eclampsia following intravenous GSNO infusion of 50-250 μ g per minute.



INTERNATIONAL SEARCH REPORT

Inv. No. PCT/GB 95/02846

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/21 A61K31/195 A61K38/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	THE LANCET, vol. 345, no. 8942, 14 January 1995 pages 124-125, A. DE BELDER ET AL. 'TREATMENT OF HELLP SYNDROME WITH NITRIC OXIDE DONOR' see the whole document ---	1-8, 10-17, 19,20
P,X	WO,A,95 02408 (SCHERING) 26 January 1995 see the whole document ---	1-4, 9-13, 18-20

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

11 March 1996

Date of mailing of the international search report

22. 03. 96

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Hoff, P

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CLINICAL AND EXPERIMENTAL PHARMACOLOGY AND PHYSIOLOGY, vol. 21, October 1994 pages 737-748, A.L.A. BOURA ET AL. 'AUTACOIDS AND CONTROL OF HUMAN PLACENTAL BLOOD FLOW'	1-4, 9-13, 18-20
Y	see the whole document	5-8, 14-17
X	--- EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, vol. 24, no. 1, January 1994 pages 76-78, B. RAMSAY ET AL. 'A NITRIC OXIDE DONOR IMPROVES UTERINE ARTERY DIASTOLIC BLOOD FLOW IN NORMAL EARLY PREGNANCY AND IN WOMEN AT HIGH RISK OF PRE-ECLAMPSIA'	1-4, 9-13, 18-20
Y	see the whole document	5-8, 14-17
X	--- AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, vol. 171, no. 4, October 1994 pages 944-948, S.P. SELIGMAN ET AL. 'THE ROLE OF NITRIC OXIDE IN THE PATHOGENESIS OF PREECLAMPSIA'	1-4, 10-13
Y	see the whole document	5-8, 14-17
X	--- AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, vol. 169, no. 5, 1993 pages 1316-1320, C. YALLAMPALLI ET AL. 'INHIBITION OF NITRIC OXIDE SYNTHESIS IN RATS DURING PREGNANCY PRODUCES SIGNS SIMILAR TO THOSE OF PREECLAMPSIA'	1-4, 10-13
Y	see the whole document	5-8, 14-17
X	--- THE LANCET, vol. 344, November 1994 pages 1458-1460, E.J. LANGFORD ET AL. 'INHIBITION OF PLATELET ACTIVITY BY S-NITROSOGLUTATHIONE DURING CORONARY ANGIOPLASTY'	19,20
Y	see the whole document	5-8, 14-17
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INTERNATIONAL SEARCH REPORT

Inventor's Name

PCT/GB 99/02846

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUROPEAN HERAT JOURNAL, vol. 12, 1992 pages 16-24, W.R. KUKOVETZ ET AL. 'CELLULAR MECHANISMS OF ACTION OF THERAPEUTIC NITRIC OXIDE DONORS'	19,20
Y	see abstract	5-8, 14-17
X	WO,A,89 12627 (BRIGHAM AND WOMEN'S HOSPITAL) 28 December 1989 see abstract see page 21, line 9 - line 27 see page 24, line 1 - page 25, line 15 see page 27, line 1 - page 29, line 28; claims; example 7	1-7, 10-16, 19,20
X	AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, vol. 154, no. 5, 1986 pages 1053-1059, D.B. COTTON ET AL. 'CARDIOVASCULAR ALTERATIONS IN SEVERE PREGNANCY-INDUCED HYPERTENSION: EFFECTS OF INTRAVENOUS NITROGLYCERIN COUPLED WITH BLOOD VOLUME EXPANSION' see the whole document	1-4, 9-13, 18-20
X	US,A,5 208 233 (KEEFER ET AL.) 4 May 1993 see abstract see column 1, line 43 - line 57 see column 8, line 9 - line 26; claims	1-4, 10-13, 19,20
A	EP,A,0 441 119 (LEVERE) 14 August 1991 see the whole document	1-20

INTERNATIONAL SEARCH REPORT

national application No.

PCT/GB95/02846

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 10-18 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-4, 10-13, 19-20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
A compound cannot be sufficiently characterised by its pharmacological profile or its mode of action as it is done by an expression like "NO donor". However, the search has been carried out and based on the compounds mentioned in claims 5-9.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on family members

International Application No.

PCT/GB 95/02846

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